Taurine Intestinal Absorption and Renal Excretion Test in Diabetic Patients: a Pilot Study

Marie Merheb, M.D; Rose T. Daher, PhD; Mona Nasrallah, M.D; Ramzi Sabra, M.D; Fuad N. Ziyadeh, M.D; and Kassem Barada, M.D

Correspondence:
Kassem Barada, M.D
Division of Gastroenterology
American University of Beirut
PO Box: 11-0236
Email: kb02@aub.edu.lb

Received for publication 4 May 2007 and accepted in revised form 12 July 2007.
There is evidence that diabetes is characterized by taurine deficiency [1-4] which has been linked to diabetic retinopathy, neuropathy and nephropathy [5-7]. Taurine is involved in neuronal modulation, osmoregulation [8] and protection against oxidative stress [9]. Its plasma levels are maintained within a normal range through protein intake and de novo synthesis is limited by the activity of hepatic cysteinesulphonic acid decarboxylase which is low in humans. Taurine depletion can rapidly occur [10] which might lead to retinal, cardiac, neural, immune and hemostatic dysfunction [4, 11-14].

The reasons for taurine deficiency in diabetes remain unclear. A decrease in the overall body pool [1,2] and/or internal redistribution between the intracellular and the extracellular compartments are possibilities. The former can be secondary to decreased oral intake, poor intestinal absorption, renal wasting or a combination of factors.

In diabetic rats, intestinal absorption of taurine is reduced (Barada, K et al., unpublished data) while urinary taurine excretion is enhanced [15]. Kidney losses in uncontrolled diabetes are aggravated by severe hyperglycemia and ketoacidosis [4]. Data are lacking, however, on urinary excretion and pharmacokinetics of taurine absorption in human diabetes with mild to moderate hyperglycemia. This pilot study was therefore conducted in patients with moderately impaired glucose control and in matched nondiabetic subjects to evaluate the pharmacokinetics of taurine absorption following an oral load and to elucidate the mechanism of taurine deficiency in diabetes.

**RESEARCH DESIGN AND METHODS**

Sixteen subjects were enrolled: 6 patients with type 2 and two with type 1 and 8 healthy subjects pair-matched for age, gender and BMI. The inclusion criteria for the patients were: age, 18 to 65 years; BMI, 20 to 35 Kg/m² and glycosylated hemoglobin (HbA1c) > 7%. We excluded patients with chronic kidney disease, cholestatic liver disease, gastroparesis, malabsorption and severe ophthalmopathy or neuropathy.

After a 10-hour fast, blood was withdrawn for plasma taurine, fasting glucose, creatinine, triglycerides and HbA1c. Height, weight, heart rate and blood pressure were measured. A baseline urine specimen was collected for creatinine, microalbumin and taurine. Then six 500 mg tablets of taurine were orally given once with water. Blood was then withdrawn every hour for 6 hours and urine was collected over the study period for taurine analysis.

Biochemical measurements were performed using established methods. The GFR values calculated by the MDRD formula [16] and the creatinine clearances based on 6-hour urine collection were similar. Taurine was determined using reversed phase chromatography [17]. For each subject, hourly and peak plasma taurine and the time to achieve peak concentration following the oral taurine load were determined. The AUC was calculated and linear regression analysis was performed on the descending part of the curve only. The rate constant (Ke) and half-life of elimination (t₁/₂) were derived from the slope of the curve (slope = -Ke/2.3 and t₁/₂ = 0.693/Ke).

The urine taurine excretion rate was expressed in µmol/h. Fractional excretion (FE) is the ratio of taurine
clearance to creatinine clearance, expressed in percentage.

Mann-Whitney test was used to compare variables between groups. $P$ values $\leq 0.05$ were considered significant (SPSS 14.0, Chicago, IL).

RESULTS

The baseline characteristics and the plasma and urine parameters of patients with diabetes and control subjects are shown in Table 1. Subjects in both groups had normal kidney function.

There was a trend towards a lower baseline plasma taurine concentration in the type 2 patients ($P=0.056$). The temporal pattern of the rise and decline in plasma taurine concentration was similar in both groups. After the taurine load, peak plasma concentration of taurine was significantly lower in diabetic subjects ($p=0.007$). The increment in plasma taurine level from baseline to the first hour (Hour 1) was lower in diabetic patients. The one-hour plasma taurine concentration was lower in diabetics than controls ($p=0.015$). Moreover, AUC was significantly lower in diabetics ($p=0.028$).

Both groups had comparable basal urine taurine levels. After the taurine load, diabetic patients had a higher urinary taurine excretion rate ($p=0.028$) and higher taurine clearance ($p<0.001$). This reflected in a doubling of the fractional excretion of taurine in the diabetic group.

DISCUSSION

Our results indicate that there is a difference in the pharmacokinetics of taurine in patients with diabetes mellitus as compared with nondiabetic matched controls. After an oral taurine load, diabetic patients have a significantly lower plasma taurine concentration at peak. This might be due, in part, to impaired renal reabsorption with enhanced urinary clearance and fractional excretion. The lower plasma taurine concentration of the diabetic group in the first hour suggests that there may also be a component of decreased net intestinal absorption in diabetes. There was a trend (although not significant) for a lower baseline plasma taurine level, consistent with previous reports.

Ingested taurine is absorbed in the small intestine via its receptor (TAUT) [18] and is then distributed by active uptake to many organs against a concentration gradient [18,19].

Taurine is then conjugated in the liver to bile salts or excreted by the kidneys. The final outcome of taurine homeostasis is through fecal excretion after deconjugation by the bacterial flora or renal excretion as intact molecule [19, 21-23]. In this study at similar half-life in both groups, the urinary excretion rate of taurine was higher in diabetics. The kidneys regulate the body taurine pool: a high taurine diet induces hypertaurinuria and reduces renal tubular uptake [24], and the opposite happens on low-taurine diet. At comparable GFR but lower plasma taurine concentration at each hour of assessment, the filtered load of taurine in diabetics is lower than that of controls. The higher taurine excretion rate suggests that renal tubular reabsorption is decreased in diabetes. The latter finding may be confounded to some extent by the hyperglycemia in the diabetic group (209±49 mg/dl) inducing osmotic diuresis, or alternatively may theoretically involve a decrease in the activity of the brush-border taurine transport protein in the proximal tubule of the kidney.

In experimental diabetes, taurine supplementation may improve metabolic control [25], restore the endothelium-dependent vascular relaxation [26],
improve insulin sensitivity, attenuates hypertension, prevent diabetic cardiomyopathy [27], reverse neuropathy [28] and reduce mortality [29]. Such beneficial effects may be mediated through binding of taurine to the insulin receptor [4], decreasing glucose absorption [30], and/or directly modulating hepatic glucose metabolism [31]. Human studies on taurine supplementation are thus far inconclusive [32, 33].

This is the first study to demonstrate that, after a taurine load, diabetic patients waste taurine more extensively in the urine than matched controls, and they probably have a lower rate of net intestinal absorption. The pathogenesis of the renal findings is most likely through decreased tubular reabsorption, whereas the gastrointestinal effect is likely through decreased intestinal transfer, as further supported by animal studies. It is tempting to postulate that diminution in the activity of the brush border taurine transport protein in the proximal tubule and in the luminal cell membrane of the small intestine, can account for both the enhanced renal excretion and the impaired intestinal taurine absorption. Further studies are required to test this postulate and to assess other parameters such as fecal excretion, liver utilization and tissue distribution.

ACKNOWLEDGMENTS

This study was supported by a research grant from the Medical Practice Plan at the American University of Beirut Medical Center.
REFERENCES
Table 1. Baseline characteristics, plasma and urine taurine parameters in patients with diabetes and controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=8)</th>
<th>All Controls (n=8)</th>
<th>P*</th>
<th>Type 2 Patients (n=6)</th>
<th>Controls (n=6)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ±18</td>
<td>45±15</td>
<td>0.87</td>
<td>48±18</td>
<td>48±15</td>
<td>0.9</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>3/5</td>
<td>3/5</td>
<td>-</td>
<td>1/5</td>
<td>1/5</td>
<td>-</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>8.8± 7.8</td>
<td>-</td>
<td>-</td>
<td>9.5±8.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>3/8</td>
<td>1/8</td>
<td>-</td>
<td>3/8</td>
<td>1/8</td>
<td>-</td>
</tr>
<tr>
<td>Blood Glucose (mg/dl)</td>
<td>209±49</td>
<td>89±12</td>
<td>0.001</td>
<td>187±32</td>
<td>92±13</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycosylated Hb (%)</td>
<td>8.2±1.4</td>
<td>5.5±0.5</td>
<td>&lt;0.001</td>
<td>8.6±1.2</td>
<td>5.5±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI(Kg/m²)</td>
<td>27.2±2.6</td>
<td>28±4.0</td>
<td>0.32</td>
<td>28.3±1.94</td>
<td>30.2±2.8</td>
<td>0.217</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>135±12</td>
<td>113±10</td>
<td>0.007</td>
<td>137±14</td>
<td>117±5.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>80±9</td>
<td>70±13</td>
<td>0.105</td>
<td>82.5±8.8</td>
<td>69.5±15</td>
<td>0.105</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
<td>0.77±0.18</td>
<td>0.77 ±0.15</td>
<td>0.95</td>
<td>0.8±0.2</td>
<td>0.7±0.2</td>
<td>0.744</td>
</tr>
<tr>
<td>GFR MDRD (ml/min/1.73 m²)</td>
<td>111±19</td>
<td>105±32</td>
<td>0.16</td>
<td>111±20</td>
<td>110±36</td>
<td>0.985</td>
</tr>
<tr>
<td>Baseline Plasma Taurine (µmol/l)</td>
<td>53.5±11</td>
<td>68.1±20</td>
<td>0.195</td>
<td>51.3±11</td>
<td>72.2±21</td>
<td>0.056</td>
</tr>
<tr>
<td>Plasma Concentration at One Hour (µmol/l)</td>
<td>351±120</td>
<td>621±255</td>
<td>0.017</td>
<td>335±134</td>
<td>654±291</td>
<td>0.035</td>
</tr>
<tr>
<td>Plasma Concentration at peak (µmol/l)</td>
<td>568±68</td>
<td>742±162</td>
<td>0.007</td>
<td>552±67</td>
<td>772±179</td>
<td>0.019</td>
</tr>
<tr>
<td>AUC (µmol.h/l)</td>
<td>1499.5±266</td>
<td>2119±642</td>
<td>0.028</td>
<td>1485±312</td>
<td>2173±729</td>
<td>0.059</td>
</tr>
<tr>
<td>Time to peak(h)</td>
<td>1.8±0.3</td>
<td>1.8±1.1</td>
<td>0.6</td>
<td>1.8±0.4</td>
<td>1.8±1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>T ½ (h)</td>
<td>2.3±0.7</td>
<td>2±0.61</td>
<td>0.5</td>
<td>2.5±0.8</td>
<td>1.9±0.5</td>
<td>0.241</td>
</tr>
<tr>
<td>Urine Taurine excretion rate (µmol/h)</td>
<td>1225±206</td>
<td>932±245</td>
<td>0.028</td>
<td>1266±221</td>
<td>938±279</td>
<td>0.048</td>
</tr>
<tr>
<td>Urinary Taurine Clearance (L/h)</td>
<td>4.2±0.9</td>
<td>2.4±0.5</td>
<td>&lt;0.001</td>
<td>4.5±0.8</td>
<td>2.4±0.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary Fractional excretion (%)</td>
<td>0.6±0.1</td>
<td>0.34±0.13</td>
<td>0.002</td>
<td>0.58±0.1</td>
<td>0.37±0.1</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SD for all diabetic patients (n=8) and for the ones with type 2 diabetes mellitus (n=6).

*Significant p<0.05 (Mann-Whitney test).

**GFR was estimated by MDRD method.

†AUC=Area Under the Curve; §T½=half-life. The study was approved by the Institutional Research Board at the American University of Beirut.